CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-440

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

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Approvable Package
Lexapro (escitalopram oxalate) Tablets
NDA 21-440

UF DUE DATE Thursday August 29, 2001

APPEARS THIS WAY
ON ORIGINAL

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 28, 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for
Lexpro tablets (escitalopram) for the longer-term treatment of major depressive disorder (MDD)

TO: File NDA 21-440
[**Note:** This overview should be filed with the 10-26-01 original submission.]

1.0 BACKGROUND

Escitalopram is a selective serotonin reuptake inhibitor. It is the S-enantiomer of racemic citalopram, which is currently approved and marketed for depression in an immediate release tablet, i.e., Celexa (NDA 20-822, originally approved for depression on 7-17-98). Essentially all of the serotonin reuptake blocking activity of the racemate resides in the S-enantiomer. Escitalopram was recently approved for the acute treatment of depression (8-14-02). This NDA provides data from a single study (SCT-MD-03) in support of a new claim for escitalopram tablets in the longer-term treatment MDD in a dose range of 10 to 20 mg/day.

We did not have any meetings or correspondence with Forest regarding their program for obtaining longer-term efficacy data for the MDD indication.

Since the proposal is to use the currently approved escitalopram tablet, there was no need for chemistry, pharmacology, or biopharmaceutic reviews of this supplement. The focus was on clinical data. The primary review of the efficacy and safety data was done by Karen Brugge, M.D., from the clinical group. Ohidul Siddiqui, Ph.D., from the Division of Biometrics, also reviewed the efficacy data.

The study supporting this supplement was conducted under [redacted]. The original supplement for this expanded indication was submitted 10-26-01.

We decided not to take this supplement to the Psychopharmacological Drugs Advisory Committee (PDAC).

2.0 CHEMISTRY

As escitalopram tablets are already approved, there were no CMC issues requiring review for this NDA.

3.0 PHARMACOLOGY

As escitalopram tablets are already approved, there were no pharm/tox issues requiring review for this NDA.

4.0 BIOPHARMACEUTICS

As escitalopram tablets are already approved, there were no biopharmaceutics issues requiring review for this NDA.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Study SCT-MD-03

Results from study SCT-MD-03 were submitted in support of this claim for the longer-term efficacy of escitalopram in MDD. This 53 center US study recruited adult patients who had completed either of 2 8-week studies of escitalopram in MDD (DSM-IV). These patients (n=540) were given escitalopram for an additional 8 weeks of open label treatment, starting at a dose of 10 mg/day, with a dose increase to 20 mg/day permitted for nonresponders (patients whose MADRS scores were >12 at the ends of weeks 4 and 6). At the end of week 8, responders (MADRS $\leq$ 12) were randomly assigned to double-blind treatment with either escitalopram or placebo in a 2:1 ratio. A total of n=274 patients were randomized (and met modified ITT criteria), with n=181 receiving escitalopram and n=93 receiving placebo. Patients were instructed to take the same escitalopram dose during this phase that they had been taking at the end of the 8-week open label phase, i.e., either 10 or 20 mg/day. This double-blind discontinuation phase ran for up to 36 weeks.

The primary endpoint was time to relapse, where relapse was defined as (1) an increase in the MADRS score to $\geq$ 22, or (2) withdrawal from the study due to lack of efficacy. There were a number of secondary endpoints, including crude relapse rate, however, none was designated as key secondary endpoints. The primary analysis for time to relapse was the log rank test, used to test the equality of

relapse hazards in the two groups. Kaplan-Meier curves were also estimated. Analyses were based on an ITT sample including all randomized patients who received at least 1 dose of assigned treatment and had baseline and at least one post-randomization efficacy assessment.

Patients in this study were roughly 61% female, 86% Caucasian, and the mean age was roughly 43 years.

The overall rates of discontinuation prior to reaching the 36 week nominal endpoint were as follows:

Escitalopram: 89/181 (49%)
Placebo: 62/93 (67%)

The results on the primary endpoint, time to relapse, favored escitalopram:

Hazard ratio (escitalopram vs placebo) = 0.56 (p=0.013)

The proportion relapsed by 36 weeks also favored escitalopram over placebo, but just missed statistical significance:

Escitalopram: 41/181 (23%)
Placebo: 31/93 (33%) p=0.058

Escitalopram was favored over placebo on most other secondary endpoints.

Exploratory analyses looking at the effect of age, sex, and race did not suggest that any of these factors affected the outcome.

Dr. Siddiqui performed an additional analysis of time to all cause discontinuation (i.e., relapse plus any other reason for leaving early) before reaching 36 weeks, and this analysis also strongly favored escitalopram over placebo (p=0.0023).

Comment: Both Drs. Brugge and Siddiqui considered this a positive study in support of a claim of long-term efficacy for escitalopram in MDD, and I agree.

5.1.2 Conclusions Regarding Efficacy Data

Study SCT-MD-03 demonstrated a benefit of escitalopram over placebo for the maintenance of response in patients with MDD who demonstrated a response during an initial 8 week open-label treatment period and were then observed for relapse during a 36-week followup period.

5.2 Safety Data

Dr. Brugge reviewed the safety data for study SCT-MD-03 (including data for n=181 patients exposed to escitalopram) in her review of NDA 21-323 in support of an acute claim for escitalopram for MDD, since the safety data for this study were submitted during the review cycle for that NDA. The ECG findings of interest from the entire escitalopram safety database, including postmarketing data for racemic citalopram, have also been reviewed independently by Drs. Gan and Racoosin from the Safety Group, and the reader is referred to the earlier reviews by Drs. Brugge, Gan and Racoosin, as well as my approvable and approval memos, for NDA 21-323, for the details of the safety assessment. Since none of the safety findings, including the longer-term exposure data from study SCT-MD-03 was considered an obstacle to the approval of escitalopram, this product was approved for the acute treatment of MDD and currently approved labeling addresses all of our concerns about safety, including any concerns specific to longer-term use. In summary, there were no important new safety concerns identified in association with the longer-term use of escitalopram that had not already been observed in short-term use.

5.3 Clinical Sections of Labeling

We have modified the language in the 3 sections of labeling in which the sponsor has proposed changes, i.e., Clinical Trials, Indications, and Dosage and Administration. As of 8-28-02, we reached agreement with Forest on the language for labeling.

6.0 WORLD LITERATURE

This NDA included reference to an additional 4 published papers for escitalopram (i.e, in addition to those submitted with NDA 21-323), and none contained any important new safety information regarding this product. An update on citalopram literature was also submitted to this NDA, and this included a report of an overdose case with QTc prolongation. This case is discussed in the reviews by Drs. Racoosin and Gan for NDA 21-323, referred to above.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, escitalopram is not approved for the longer-term treatment of MDD anywhere at this time.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

As noted, we did not take this supplement to the Psychopharmacological Drugs Advisory Committee (PDAC).

9.0 DSI INSPECTIONS

Two sites from study SCT-MD-03 (Doraiswamy and Heiser) were inspected. While there was a concern about ECG data coming from the Doraiswamy site, apparently due to incorrect use of the ECG machine, there was no concern about the efficacy data coming from either site. The ECG issue has been resolved in the review of the NDA for the acute claim in MDD.

10.0 LABELING AND APPROVAL LETTER

10.1 Labeling Attached to Approval Package

Our mutually agreed upon labeling for this new claim is included in the approval letter.

10.2 Foreign Labeling

To my knowledge, escitalopram is not approved for the longer-term treatment of MDD anywhere at this time.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Forest has submitted sufficient data to support the conclusion that escitalopram is effective and acceptably safe in the longer-term treatment of MDD. Since we have now reached agreement with Forest on final labeling, I recommend that we issue the attached approval letter with the agreed upon labeling language for this expanded claim.

cc:
Orig NDA 21-440
HFD-120
HFD-120/TLaughren/RKatz/KBrugge/PDavid

DOC: MEMECTLT.AP1

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
8/28/02 10:58:23 AM
MEDICAL OFFICER

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NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-440 _____ _____

Drug Lexapro (escitalopram) 5, 10, and 20 mg Tablets Applicant Forest

RPM Paul David Phone x4-5530

■505(b)(1)
☐505(b)(2) Reference listed drug _____

☐Fast Track ☐Rolling Review Review priority: ■ S ☐P

Pivotal IND(s) —

Application classifications:
Chem Class 2020100
Other (e.g., orphan, OTC) _____

PDUFA Goal Dates:
Primary 8-29-02
Secondary 8-29-02

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ■User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐User Fee Exemption

- Action Letter..... ■AP ☐AE ☐NA

- Labeling & Labels
  FDA revised labeling and reviews..... X
  Original proposed labeling (package insert, patient package insert) X
  Other labeling in class (most recent 3) or class labeling..... N/A
  Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) ■ No
  Immediate container and carton labels ..... N/A
  Nomenclature review ..... N/A

- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ■ is not on the AIP.

  Exception for review (Center Director's memo)..... N/A
  OC Clearance for approval..... N/A

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) — ■ Materials requested in AP letter
- Post-marketing Commitments — N/A
  - Agency request for Phase 4 Commitments.....
  - Copy of Applicant's commitments .....
- Was Press Office notified of action (for approval action only)?..... — ☐ Yes ■ No
  - Copy of Press Release or Talk Paper.....
- Patent
  - Information [505(b)(1)] ..... — X
  - Patent Certification [505(b)(2)].....
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....
- Exclusivity Summary ..... — X
- Debarment Statement ..... — X
- Financial Disclosure
  - No disclosable information ..... — X
  - Disclosable information – indicate where review is located .....
- Correspondence/Memoranda/Faxes ..... — X
- Minutes of Meetings ..... — X
  - Date of EOP2 Meeting None
  - Date of pre NDA Meeting 11-14-00
  - Date of pre-AP Safety Conference N/A
- Advisory Committee Meeting ..... — N/A
  - Date of Meeting .....
  - Questions considered by the committee .....
  - Minutes or 48-hour alert or pertinent section of transcript .....
- Federal Register Notices, DESI documents ..... — N/A

CLINICAL INFORMATION: — **Indicate N/A (not applicable), X (completed), or add a comment.**

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) ..... — X
- Clinical review(s) and memoranda ..... — X
- Safety Update review(s) ..... — N/A
- Pediatric Information
  - Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
  - Pediatric Page..... — X
  - ☐ Pediatric Exclusivity requested? ☐ Denied ■Granted ☐Not Applicable — 7-12-02

- ♦ Statistical review(s) and memoranda X
- ♦ Biopharmaceutical review(s) and memoranda..... N/A
- ♦ Abuse Liability review(s) ..... N/A
  Recommendation for scheduling .....
- ♦ Microbiology (efficacy) review(s) and memoranda ..... N/A
- ♦ DSI Audits X
  ■Clinical studies ☐ bioequivalence studies .....

CMC INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- ♦ CMC review(s) and memoranda ..... N/A
- ♦ Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/A
- ♦ DMF review(s) ..... N/A
- ♦ Environmental Assessment review/FONSI/Categorical exemption ..... N/A
- ♦ Micro (validation of sterilization) review(s) and memoranda ..... N/A
- ♦ Facilities Inspection (include EES report) N/A
  Date completed 11-29-01 ..... ☐Acceptable ☐Not Acceptable
- ♦ Methods Validation ..... ☐ Completed ☐ Not Completed

PRECLINICAL PHARM/TOX INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- ♦ Pharm/Tox review(s) and memoranda ..... N/A
- ♦ Memo from DSI regarding GLP inspection (if any) ..... N/A
- ♦ Statistical review(s) of carcinogenicity studies ..... N/A
- ♦ CAC/ECAC report ..... N/A

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Paul David
8/28/02 10:53:07 AM

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 21-440 SUPPL # _____
Trade Name Lexapro Generic Name: escitalopram oxalate
Applicant Name Forest Pharmaceuticals HFD-120

Approval Date 8-29-02

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X_/

      If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /X__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

d) Did the applicant request exclusivity?

YES / __/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /_X_/ NO /___/

Pediatric studies were conducted using the racemate formulation, Celexa (citalopram HBr) tablets, and submitted as pediatric efficacy supplements to NDA 20-822/SE5-016 (Celexa tablets) and 21-046/SE5-002 (Celexa solution). Pediatric exclusivity was granted for these applications on 7-12-02.

In a ruling by General Counsel, it was decided that pediatric exclusivity would extend to the enantiomer formulation, escitalopram, once approved if the racemate, citalopram, was granted pediatric exclusivity. The Agency has approved the parent NDA 21-323 in an approval letter dated 8-14-02, and the relapse prevention NDA (Type 6 NDA) was approved on 8-29-02. Pediatric exclusivity was granted for the racemate, citalopram, in an action dated 7-12-02.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form,
strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /_X_/ NO / __/

If yes, NDA # 21-323 Drug Name Lexapro (escitalopram oxalate) Tablets

***At the time of submission of this clinical trial providing for a relapse prevention study in major depressive disorder (MDD), the Agency had, as yet, not taken a final action on the

parent NDA, 21-323, demonstrating short-term efficacy in major depressive disorder (MDD). Therefore, Forest had to submit this application, NDA 21-440, as a Type 6 NDA.
I have therefore filled out the 3-year exclusivity portion of this form.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 21-323 AP Date 8-14-02

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing <u>any one</u> of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally

know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # SCT-MD-03 (Relapse prevention study)

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /__/ NO /_X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study #
NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study # _SCT-MD-03_____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

_ YES /X__/ NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

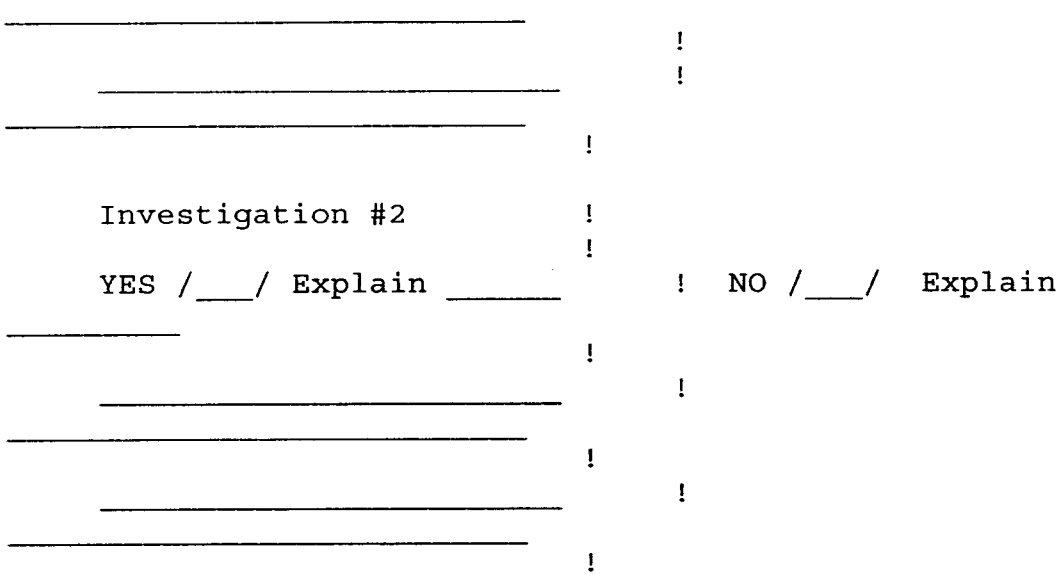
_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____



(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain:

_____

_____ _____

Signature of Preparer Date
Title:_____

_____ _____

Signature of Office of Division Director Date

cc:
Archival NDA 21-440
HFD-120/Division File
HFD-120/David
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
8/29/02 03:21:07 PM

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-440_____ Supplement Type (e.g. SE5): _____ Supplement Number:_____

Stamp Date: 10-26-01 Action Date: 8-29-02

HFD-120__ Trade and generic names/dosage form: Lexapro (escitalopram oxalate) Tablets

Applicant: Forest Therapeutic Class: 2020100 (Major Depressive Disorder [MDD])

Indication(s) previously approved: Short term treatment of MDD under NDA 21-323

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Relapse Prevention Study (maintenance treatment)

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- ■ No: Please check all that apply: ____Partial Waiver ____Deferred X___Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

ection A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._7____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._17____ Tanner Stage_____

Comments:

Pediatric studies were conducted using the racemate formulation, Celexa (citalopram HBr) tablets, and submitted as pediatric efficacy supplements to NDA 20-822/SE5-016 (Celexa tablets) and 21-046/SE5-002 (Celexa solution). Pediatric exclusivity was granted for these applications on 7-12-02.

In a ruling by General Counsel, it was decided that pediatric exclusivity would extend to the enantiomer formulation, escitalopram, once approved if the racemate, citalopram, was granted pediatric exclusivity. The Agency has approved the parent NDA 21-323 in an approval letter dated 8-14-02, and the relapse prevention NDA (Type 6 NDA) will be approved on 8-29-02. Pediatric exclusivity was granted for the racemate, citalopram, in an action dated 7-12-02.

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

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Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 301-594-7337

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/s/

Paul David
8/29/02 08:32:58 AM
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Number of Pages Redacted 11

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

CLINICAL INSPECTION SUMMARY

DATE: June 19, 2002

TO: Paul David, R.Ph., Senior Regulatory Project Manager
Karen Brugge, M.D., Medical Officer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Antoine El-Hage, Ph.D., Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

FROM: Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 21-440

APPLICANT: Forest Laboratories, Inc.

DRUG: Escitalopram Oxalate Tablets

THERAPEUTIC CLASSIFICATION: Type S, Standard Review

INDICATION: Major Depressive Disorder Relapse Prevention

CONSULTATION REQUEST DATE: January 14, 2002

ACTION GOAL DATE: June 29, 2002

I. BACKGROUND:

Escitalopram (Lu 26-054) is the S-enantiomer of the selective serotonin reuptake inhibitor citalopram, which is currently marketed under the brand name of Celexa for depression. In 2001, the sponsor has submitted the use of escitalopram in major depressive disorder under NDA 21-323. In this NDA 21-440, the sponsor has requested the use of escitalopram in relapse prevention of major depressive disorder.

Inspection assignments were issued on February 28, 2002 for two domestic sites, Drs. Doraiswamy and Heiser for Protocol SCT-MD-03. According to protocol SCT-MD-03, the

subjects received flexible dose of escitalopram for 8 weeks (open label phase) followed by fixed dose (max: 20mg/day) or placebo-control for 36 weeks (double blind phase) for prevention of depression relapse. The inspection was for the purpose of validating data in support of pending NDA 21-440.

II. RESULTS (by site):

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Doraiswamy	Durham	NC	02-28-2002	05-20-2002	VAI*
Heiser	Newport Beach	CA	02-28-2002	06-17-2002	NAI

*Final classification pending; the draft letter is currently with Office of General Counsel (GC) for review.

Doraiswamy, M.D.

At this site, 12 subjects who completed the lead-in study, SCT-MD-01, continued into protocol SCT-MD-03 with 4 subjects completing the study. The discontinuation reasons included lack of efficacy (3 subjects), protocol violation (1 subject) and personal reasons/withdrew consent (4 subjects).

An audit of 12 records was conducted. Signed and dated informed consents were present for all the participants.

Inspectional findings revealed identical EKG tracings for the following subjects in the lead-in-study, SCT-MD-01 and study 03.

- 2/3/2000 EKG and 2/3/2000 EKG
- 2/9/2000 EKG and 2/10/2000 EKG
- 3/15/2000 EKG, 3/17/2000 EKG and s 3/21/2000 EKG
- 3/24/2000 EKG and 4/11/2000 EKG
- 5/19/2000 EKG, 5/22/2000 EKG and 5/26/2000 EKG

It appeared that EKG memory clear button error was identified after the FDA investigator noticed identical tracings obtained for 2 to 3 consecutive subjects in five separate occasions. Specifically, EKG user manual given to the sites and the sponsor files specified that clear memory button be held for 5 seconds to erase prior EKG while it was needed for 30 seconds. Each pair or trio of identical tracings occurred in sequence, which suggested the device error.

According to the protocol (SCT-MD-03), EKG measurements were required at baseline visit 1(final visit of the lead-in study: SCT-MD-01), visit 5 (week 6 of the open-label phase) and visit 16 (week 44 of double-blind phase) or upon early termination when the patient discontinued prior to week 44. As per the study procedure, all baseline EKGs

were processed by [redacted] and the reports were sent to the study site for the investigator's evaluation. EKGs performed at other time points were reviewed at each center.

At this site, twelve subjects enrolled in the protocol SCT-MD-03 from the lead-in study SCT-MD-01. The EKG problem was identified in 11 subjects as per FDA-483. In Dr. Doraiswamy's written response dated April 18, 2002, it was stated that he has reviewed every EKG done in both SCT-MD-01 and SCT-MD-03. Among the 39 EKGs done, he discovered that there were 7 duplicate traces of 5 EKGs. Of these 7 duplicate tracings, 3 occurred at the screening visit of SCT-MD-01. Of these 3, one subject was a screen failure who never received the study drug, the second subject had normal EKG at other time points done with different machines and the third had no history of cardiac disease. All 4 patients with potential duplicate traces at end point of SCT-MD-01 had normal EKGs at entry and at least one also had normal EKGs at other time points using other machines. No subject identifiers were mentioned and no assurance that these EKGs are valid at this site.

Dr. Doraiswamy has taken appropriate steps by informing the sponsor and the IRB in regards to this matter. However, it appeared that he did not evaluate the subjects' EKGs thoroughly as he did not recognize these identical tracings until it was pointed by the FDA investigator. This would have had an effect on subjects' safety.

In his response to FDA-483 inspectional findings, it was also noted that "the sponsor verbally informed me that they are examining all EKG done using this device in this study and that their initial review showed that one or more duplicates were also found at other sites." If this issue is of concern, I suggest that the Review Division should check with the sponsor, to examine their safety database for similar problem at other sites and report to the FDA.

Overall, the efficacy data appear acceptable. DSI recommends excluding the EKG safety data generated at this site.

Heiser, M.D.

There were 17 subjects entered into the study; 12 of which were randomized and 7 subjects completed the study. An audit of 17 records was conducted. No significant deviation from regulation was noted. Signed and dated informed consents were present for participants. Data appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Overall, the efficacy data from these two domestic sites appear acceptable for use in support of the pending NDA.

As stated above, DSI recommends the Review Division to consider excluding the EKG safety data generated at Dr. Doraiswamy's site and checking with sponsor if the safety database contains similar problems with EKGs done at other sites.

Recently, DSI has investigated eResearch to find the extent of this problem in relation to other studies. The Review Division will be informed accordingly as additional information is obtained.

There was no limitation to these inspections.

[Note: The review and evaluation of the Heiser audit was based on the FDA Investigator's Preliminary Summary of Findings. Should the EIR and exhibits from the audit, when received, contain additional information that would significantly effect the classification or have an impact on the acceptability of the data, we will inform the review division accordingly.]

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAIr= Deviation(s) form regulations, response requested. Data acceptable
OAI = Significant deviations for regulations. Data unreliable
Pending = Inspection not completed

Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

cc:
NDA 21-440
Division File
HFD-45/Program Management Staff (electronic copy)
HFD-47/c/r/s
HFD-47/Khin
HFD-47/Friend
HFD-45/RF

rd:NK:06/19/02

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/s/

Michele Lackner
6/27/02 12:12:56 PM
TECHNICAL
Original signed by Drs. ElHage and Khin on 6/20/02.

APPEARS THIS WAY ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

David
Public Health Service

Food and Drug Administration
Rockville MD 20857

Jon F. Heiser, M.D.
1601 Dove Street Suite 290
Newport Beach, California 92660

AUG 22 2002

Dear Dr. Heiser:

Between May 28 and 31, 2002, Ms. Kirsten S. Tharp, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol SCT-MT-03 entitled: "Placebo-Controlled Evaluation of the Safety and Efficacy of Lu 26-054 in the Prevention of Depression Relapse") of the investigational drug escitalopram, performed for Forest Laboratories, Incorporated. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to ensure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to FDA regulations governing your conduct of clinical investigations and the protection of human subjects.

We appreciate your cooperation with Investigator Tharp during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003694508
Field Classification: NAI
Headquarters Classification:
__X__1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

cc:
HFA-224
HFD-120 Doc.Rm. NDA 21-440
HFD-120 Review Div.Dir. Katz
HFD-120 MO Brugge
HFD-120 PM David
HFD-45 Reading File
HFD-47 c/r/s GCP File #10682
HFD-47 Khin/Friend
HFR-PA252 DIB Stokke
HFR-PA2565 BIMO Koller
HFR-PA2585 Field Investigator Tharp

r/d:BRF:(8/15/02)
reviewed:AEH:**(08/16/02)**
f/t:ml:**(08/16/02)**
O:\BRF\Investigator NAI\Heiser.8.02

Reviewer Note to Rev. Div. M.O.